REMARKS

Claims 25-48 are pending in this application for the Examiner's review and consideration. The pending claims were renumbered to properly begin at claim 25. As noted by the Examiner, in the previous amendment, claims 1-24 were canceled and the new claims were numbered beginning with claim number 26 rather than claim number 25. Accordingly, the claims have been renumbered and amended to show proper dependency. Independent claims 25 and 34 were further amended to replace the recitation that the composition is an "injectable composition" with the recitation that the composition is "formulated as a composition for administration to a mammal by injection" (*See*, Specification, ¶ [0009]). No new matter is added by these new claims so that their entry at this time is warranted.

Applicants have not canceled withdrawn method claims 38-48. The MPEP states that when:

> The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder .

(*See*, MPEP ¶ 806.05(h) and Form paragraph 8.21.04). Accordingly, because process of use claims 38-48 depend from independent product claim 25, Applicants respectfully request that these process of use claims be rejoined if product claim 25 is found allowable.

THE REJECTION UNDER 35 U.S.C. § 103(A)

Claims 25-31 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. patent no. 5,336,664 to Camaggi *et al.* ("Camaggi") in view U.S. patent no. 4,872,111 to Nagy ("Nagy") for the reasons set forth on pages 4-6 of the Office Action. Applicant respectfully traverses.

Camaggi discloses herbicides for agricultural use (*See*, Camaggi, column 1, lines 6-10). The structure of the herbicides is provided at column 1, line 11 to column 2, line 30 of Camaggi. The Examiner asserts that Camaggi discloses florfenicol propionate and florfenicol acetate are useful in the compositions for agricultural use as a herbicide. The Examiner further asserts that

Camaggi discloses formulating the compounds with the pharmaceutical carrier water, that the compositions can comprise more than one compound of formula I, and that combining two or more compounds of formula I are useful because it gives complementary herbicidal characteristics.

Nagy discloses an applicator device for injecting liquid additives into the soil. The Examiner asserts it would have been obvious to formulate the compositions of Camaggi, comprising mixtures of one or more compounds of formula I, as an injectable herbicide because Nagy teaches that the injectable applicator disclosed therein permits accurate measurement of the amount of herbicide fed to the soil.

As the Examiner is aware the proper inquiry for obviousness is whether the reference discloses each and every feature of the claim (*See*, MPEP, ¶ 1242) and whether the references suggest the invention and provides one of ordinary skill in the art with a reasonable expectation of success. *In re Vacek*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991); *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988).

Applicant respectfully submits that the combination of Camaggi and Nagy do not render claims 25-31 obvious because the references do not discloses each and every feature of the claims, suggest the invention, or provide a reasonable expectation of success. Initially, Applicant respectfully submits that the Examiner has misconstrued the phrase "injectable composition" used in claim 25 prior to claim 25 being amended. Specifically, the Examiner did not recognize that the phrase "injectable composition" refers to a composition for administration to a mammal. The specification, however, clearly states that:

> By "injectable" is meant a composition of formulation that is suitable for placing into a syringe and *injecting into the mammalian body.*

(*See*, specification, ¶ [0009], emphasis added). Accordingly, the phrase should not be construed to encompass injection into the soil, as was done by the Examiner. Although in Applicant's opinion it was not necessary to do so in view of the specification, Applicant has amended independent claim 25 (and 34) to more clearly recite that the composition is "formulated as a composition for administration to a mammal by injection."

There is absolutely no disclosure in Camaggi or Nagy of a composition that is injectable, *i.e.*, formulated as a composition for administration to a mammal by injection. Camaggi simply discloses a composition that is herbicide, *i.e.*, for killing weeds. There is, however, no disclosure or suggestion that the compositions disclosed therein could be formulated for administration to a mammal, much less by injection. Similarly, Nagy discloses a device for applying herbicides to soil. Again, there is no disclosure or suggestion that the compositions could be formulated for administration to a mammal, much less by injection.

The requirements of a composition for application to weeds, *i.e.*, herbicidal compositions, are completely different from those of a composition "for administration to a mammal by injection." For example, compositions for administration to a mammal by injection, unlike herbicidal compositions, cannot include solid materials, cannot be highly viscous, typically must be sterile, and must be capable of being administered without causing tissue damage or causing severe pain. Both Camaggi and Nagy are silent regarding these differences.

Furthermore, although Camaggi discloses that the compositions can comprise more than one compound of formula I and that combining two or more compounds of formula I are useful because it gives complementary herbicidal characteristics, there is absolutely no disclosure or suggestion that such a combination could, or should, be formulated for administration to a mammal. Because a mixture of two compounds can be formulated as a herbicide that has complementary herbicidal characteristics provides no suggestion, motivation, or reasonable expectation of success that such a composition could be formulated for administration to a mammal, much less by injection.

The claimed composition, which includes the combination of a first ester prodrug of florfenicol and a second ester prodrug of florfenicol formulated as a composition for administration to a mammal by injection, however, advantageously provides a composition that, when administered to the mammal, allows for an "initial burst" followed by a slower more sustained release to provide a better pharmacokinetic profile (*See*, Specification, ¶ [0028] - [0029], [0036], and Example 10, ¶ [0058]). The claimed composition provides a product that is a therapeutically more effective product and a safer product.

There is absolutely no disclosure or suggestion in Camaggi or Nagy to formulate a first

ester prodrug of florfenicol and a second ester prodrug of florfenicol as a composition for administration to a mammal by injection. The mere disclosure of herbicide formulations provides no motivation to make a composition for administration to a mammal, much less by injection, and provides no reasonable expectation that such a composition would be effective for administration to mammals, much less that the composition would provide a therapeutically more effective product and a safer product. For the above reasons, Applicant respectfully submits that claims 25-31 are not rendered obvious by Camaggi or Nagy, either alone or in combination. Accordingly, Applicant respectfully requests that the rejection of claims 25-31 as being rendered obvious be reconsidered and withdrawn.

Claims 32-33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Camaggi in view Nagy and further in view of U.S. published application no. US 2002/0065198 to Highsmith *et al.* ("Highsmith") for the reasons set forth on pages 6-7 of the Office Action. Applicant respectfully traverses.

Camaggi and Nagy were applied by the Examiner for the reasons set forth above. The Examiner acknowledged that Camaggi and Nagy do not teach propylene glycol. The Examiner, however, cites Highsmith as disclosing concentrated glycol suspensions of agricultural materials that have superior stability and asserts it would have been obvious to employ propylene glycol in Camaggi's formulation as modified by Nagy.

As discussed above, Camaggi and Nagy do not render the claims obvious. Highsmith does not remedy the deficiencies in Camaggi and Nagy. The mere disclosure in Highsmith that agricultural solids can be formulated as a suspension in glycols does not remedy the deficiencies in Camaggi and Nagy. Indeed, Highsmith by disclosing suspensions, which include solid particles, discloses compositions that are not suitable for administration to a mammal by injection. Therefore, Highsmith actually teaches away from the claimed composition that is "formulated as a composition for administration to a mammal by injection." For the above reasons, Applicant respectfully submits that claims 32-33 are not rendered obvious by Camaggi, Nagy, or Highsmith, either alone or in combination. Accordingly, Applicant respectfully requests that the rejection of claims 32-33 as being rendered obvious be reconsidered and withdrawn.

Claims 34-37 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. published application no. US 2004/0198704 to Shuster *et al.* ("Shuster") for the reasons set forth on pages 7-9 of the Office Action. Applicant respectfully traverses.

The Examiner asserts that Shuster discloses a formulation comprising a compound having the structural formula of florfenicol and its ester derivatives. The Examiner acknowledges that Shuster does not explicitly teach florfenicol butyrate, as required by independent claim 34. The Examiner then asserts that it would have been obvious to formulate florfenicol butyrate and, absent evidence to the contrary, there would have been a reasonable expectation of success at formulating any one of the ester derivatives, including florfenicol butyrate, by the teaching of Shuster. The Examiner acknowledged that Example 8 and FIG 8 of the specification compares the administration of florfenicol butyrate to NuFlor, but asserts that this does not correlate with the surprising an unexpected results. Applicant respectfully traverses.

There is absolutely no disclosure in Shuster of the advantageous properties of a composition comprising florfenicol butyrate and the claimed pharmaceutically acceptable solvents wherein the composition is formulated as a composition for administration to a mammal by injection, as recited in independent claim 34. Applicant has unexpectedly discovered that injectable compositions containing florfenicol butyrate are superior to compositions that contain florfenicol or other prodrugs of florfenicol. In particular, when administered to a cat, florfenicol butyrate compositions are superior at providing an effective level of florfenicol in the serum while reducing toxicity. Unlike other prodrugs of florfenicol that were studied, when florfenicol butyrate is administered to a cat and samples of the cat's serum analyzed over time, there is detected in the serum effective levels of florfenicol but undetectable levels of the prodrug (*i.e.*, the florfenicol butyrate). Without wishing to be bound by theory, Applicant believes that this is due to florfenicol butyrate having a unique release rate and metabolism rate by esterases so that when a composition comprising florfenicol butyrate and a pharmaceutically acceptable solvent is administered to a cat it provides a serum level of florfenicol that is unexpectedly safe and effective.

Contrary to the Examiner's assertions, the superiority of florfenicol butyrate compared to

NuFlor (*i.e.*, florfenicol) is clearly supported by the specification and Applicant's Declaration submitted with the previous Office Action ("Declaration"). As acknowledged by the Examiner, FIG 8 clearly shows that NuFlor and florfenicol butyrate have different distribution profiles. The Examiner, however, asserts that these different distribution profiles do not correlate with the unexpected pharmacological activity. Example 8 and FIG 8, as discussed in the Declaration at paragraph 6, show that florfenicol butyrate has a better pharmacological profile than NuFlor. Specifically, it has a lower C_{max} and a greater AUC. Moreover, contrary to the Examiner's assertion, these results do correlate with the unexpected reduced toxicity of florfenicol butyrate compared to NuFlor demonstrated in the Declaration. Specifically, the Declaration shows that 2 cats administered NuFlor at 120 mg/kg by subcutaneous injection had adverse reactions. In contrast, the two cats administered florfenicol butyrate at 120 mg/kg by subcutaneous injection had no adverse reactions. This is believed to be due to the better pharmacological profile of florfenicol butyrate compared to NuFlor (Declaration, ¶ 8). Specifically, the smaller C_{max} for florfenicol butyrate compared to NuFlor is believed to account for the reduce adverse reactions without compromising efficacy because florfenicol butyrate has a larger AUC compared to NuFlor. Indeed, the larger AUC for florfenicol butyrate is expected to provide better efficacy.

The Examiner asserts that the comparison of "florfenicol butyrate compared to NuFlor resulting in less toxic effect due to its better pharmacological profile cannot be determined because there is no statistically significant side by side compared numeric data comparing severity of adverse effects in [sic, of the] two active compounds." Applicant respectfully submits that one of ordinary skill in the art looking at FIG 8 would readily recognize that the smaller C_{max} and larger AUC for florfenicol butyrate compared to NuFlor is advantageous and would be expected to lead to a better therapeutic profile. Indeed, the data in Example 8 and FIG 8 is a direct comparison of florfenicol butyrate with NuFlor. Furthermore, the error bars in FIG 8 clearly show that the difference between florfenicol butyrate and NuFlor is significant. Moreover, Applicant did conduct a direct *in vivo* comparison of florfenicol butyrate and NuFlor to show the superiority of florfenicol butyrate. Applicant described this study in his Declaration. Applicants Declaration clearly states that 2 cats administered NuFlor showed adverse effects and 2 cats administered florfenicol butyrate had fewer adverse effects (Declaration, ¶ 6). Applicant respectfully submits that the evidence provided in Example 8 and FIG 8, particularly when combined with the evidence provided in the Declaration, clearly shows the unexpected

superiority of injectable florfenicol butyrate compositions compared to injectable NuFlor compositions. Such unexpected results are not taught or suggested by Shuster. There is simply no disclosure or suggestion in Shuster to select florfenicol butyrate from the laundry list of florfenicol like compounds disclosed in Shuster or the unexpected benefits of an injectable composition comprising florfenicol butyrate. For the above reasons, Applicants respectfully request that claims 34-37 are not rendered obvious by Shuster. Accordingly, Applicant respectfully requests that the rejection of claims 34-37 as being rendered obvious be reconsidered and withdrawn.

CONCLUSIONS

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicant respectfully requests a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite eventual allowance of the claims.

No fee is believed to be due for this submission. Should any additional fees be required, please charge the required fees to Kenyon & Kenyon deposit account no. 11-0600.

Respectfully submitted,

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